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(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB1-ANTAGONISTIC ACTIVITY

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring which are potent antagonists of the cannabis CB_1-receptor.The compounds have the general formula (I) wherein- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl or phenyl which may be substituted with halogen or methoxy,- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino- R_4 represents phenyl which may be substituted with 1 or 2 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)and tautomers, prodrugs and salts thereof.These enantiomers are much more potent and selective antagonists of the cannabis CB_1-receptor, than the other enantiomer.

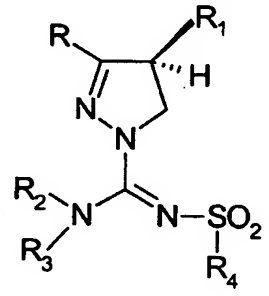
4,5-Dihydro-1H-pyrazole derivatives having CB_1-antagonistic activity

The present invention relates to a group of novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydropyrazole ring, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.
The above mentioned (4S)-4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB_1) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors,* Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB_1 receptors in the brain, in combination with the strictly peripheral localisation of the CB_2 receptor, makes the CB_1 receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in

1995. AM-630 is a CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med.Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB_1 receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1).

It has now surprisingly been found that the novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



(I)

wherein

- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R_4 represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and alkyl (1-3 C)

are much more potent and selective antagonists of the cannabis CB_1-receptor, than the correspondence R-enantiomer.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB_1 receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1 receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

The invention relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

The compounds can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

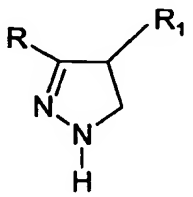
The compounds of the invention having formula (III) (*vide infra*) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the racemic compounds according to the present invention is the following:

Synthesis route A

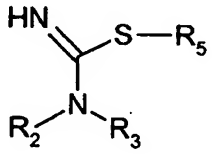
Step 1 of route A

Reaction of a compound having formula (III)



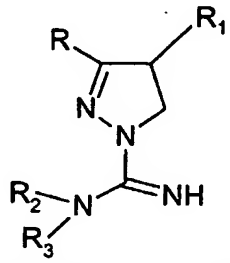
(III)

with a compound having formula (IV)



(IV)

wherein R_5 represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



(V)

wherein the symbols have the meanings as mentioned above. Compounds having formula (V) wherein R, R_1, R_2 and R_3 have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylating agent. Examples of such guanylating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylating agent. Examples of such protected guanylating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).

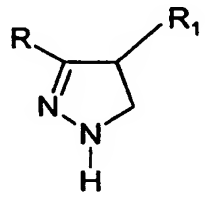
Step 2 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula R_4-SO_2X, wherein R_4 has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile.

Synthesis route A1

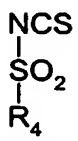
Step 1 of route A1

Reaction of a compound having formula (III)



(III)

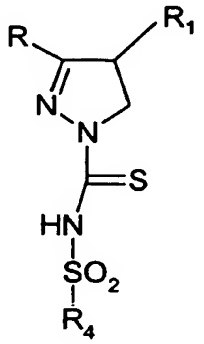
with a thioisocyanate derivative having formula (VI) .



(VI)

This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) are new.



(VII)

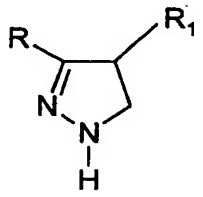
Step 2 of route A1

Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example $HgCl_2$, gives a compound having formula (I) This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

Synthesis route A2

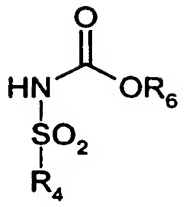
Step 1 of route A2

Reaction of a compound having formula III



(III)

with a carbamate ester derivative having formula (VIII).

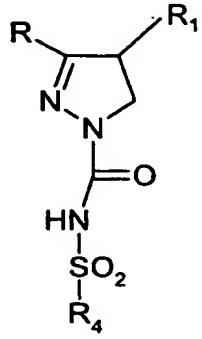


(VIII)

wherein R_6 represents a lower alkyl group, for example methyl.

This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

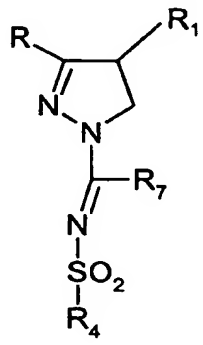
This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) are new.



(IX)

Step 2 of route A2

Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl_5, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X).



(X)

wherein R_7 represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) and wherein R_7 represents a halogen atom are new.

Step 3 of route A2

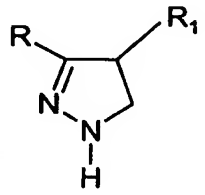
Reaction of a compound having formula (X) with an amine gives a compound having formula (I).

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

Synthesis route A3

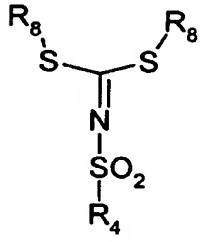
Step 1 of route A3

Reaction of a compound having formula III



(III)

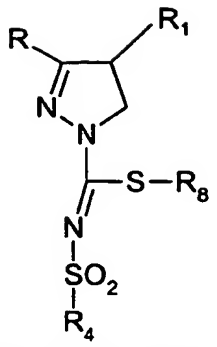
with a dithioimidocarbonic ester derivative having formula (XI) .



(XI)

wherein R_8 represents a C_{1-3} alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.



(XII)

This reaction gives a carboximidothioic ester derivative having fomula (XII).

Compounds having formula (XII) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) and wherein R_8 represents a C_{1-3} alkyl group are new.

Step 2 of route A3

Reaction of a compound having formula (XII) with an amine gives a compound having formula (I).

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl

chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.55 gram, 72 % yield). Melting point: 214-215 °C

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamidine: Melting point: 155-156 °C

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 221-222 °C

Example II

N^1,N^1-Dimethyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo*, dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na_2SO_4. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N^1-dimethyl-N^2-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.

Example III

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-tert-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-

carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

N-Methyl-N'-((3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl - 1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.

N-Propyl-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 129-138 °C.

N-(2-Propyl)-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.

N-(2-Propyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1-Ethyl-N^1-methyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.

N^1-Ethyl-N^1-methyl-N^2-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.

N^1,N^1-Dimethyl-N^2-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.

N^1,N^1-Dimethyl-N^2-((3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.

N^1,N^1-Dimethyl-N^2-((3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.

N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.

N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1,N^1-Dimethyl-N^2-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point:148-151 °C.

N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

Example IV

(-)-(4S)-N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

(-)-(4S)-N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (7.16 gram, 0.0147 mol)) ($[\alpha^{25}_D]$ = -150°, c = 0.01, MeOH) (melting point: 169-170 °C) was obtained via chiral chromatographic separation of racemic N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (18 gram, 0.037 mol) using a Chiralpak AD, 20 µm chiral stationary phase. The mobile phase consisted of a mixture of hexane/ethanol (80/20 (v/v)) and 0.1 % ammonium hydroxide (25 % aqueous solution).

In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

(-)-(4S)-N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -126 °, c = 0.01, $CHCl_3$); Melting point: 172-175 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

(-)-(4S)-N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -132 °, c = 0.01, $CHCl_3$); Melting point: 218-224 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

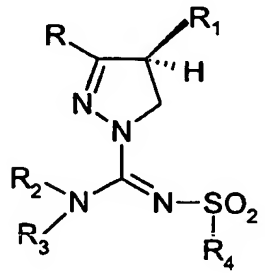
(-)-(4S)-N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -131 °, c = 0.01, $CHCl_3$); Melting point: 157-160 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

(-)-(4S)-N^1,N^1-Dimethyl-N^2-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -88 °, c = 0.01, MeOH); Melting point: Amorphous. Stationary phase: Chiralpak AD. Mobile phase: Ethanol.

(-)-(4S)-N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -129 °, c = 0.01, MeOH); Melting point: Amorphous. Chiralpak AD. Mobile phase: Methanol.

Claims

1. The enantiomer having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of a compound of formula (I)



(I)

wherein

- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R_4 represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)

and tautomers, prodrugs and salts thereof.

2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R_1 is phenyl, R_2 is hydrogen, R_3 is methyl and R_4 represents 4-chlorophenyl, and salts thereof.

3. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.

4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.

5. Process for the preparation of compounds having formula I, characterized in that the racemic mixture of a compound having formula I is separated into the levorotatory and the dextrorotatory enantiomers.

6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

7. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

8. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 02/03079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/06 C07D401/04 A61K31/415 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2002	25/06/2002

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INTERNATIONAL SEARCH REPORT

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